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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,983	11/28/2000	Scott A. Waldman	TJU-2444	8378

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,983	WALDMAN, SCOTT A.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-49* is/are pending in the application.

4a) Of the above claim(s) *24-26,29,33-35 and 37-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23, 27-28, 30-32, and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

The election filed June 26, 2002 (Paper No. 8) in response to the Office Action of March 27, 2002 is acknowledged and has been entered. Applicant has elected Group V (Claims 23 and 27-28, 30-32, and 36). It is assumed for examination purposes that this election was made without traverse since applicant's did not argue the restriction requirement.

Claims 23-49 are pending.

Claims 24-26, 29, 33-35, and 37-49 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 23, 27-28, 30-32, and 36 are currently under consideration.

Species Election

Additionally, Claim 30 is generic to a plurality of disclosed patentably distinct species comprising the plurality of agents listed in Claim 30, i.e., methotrexate, diphtheria toxin, abrin, cobra venom factor, etc.

The products of the above species represent separate and distinct molecules with different structures and functions such that one species could not be interchanged with the other. As such, each species would require different searches and the consideration of different patentability issues.

During a telephone conversation with David Cherry on October 4, 2002 a provisional election was made to prosecute the species of 5-4 fluorouracil. Affirmation of this species election must be made by applicant in replying to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 27-28, 30-32, 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of treating an individual suspected of suffering from colorectal cancer comprising administering to said individual an therapeutically effective amount of a pharmaceutical composition comprising an ST receptor ligand, an active agent that

causes cell death, and a pharmaceutically acceptable carrier or diluent. The claims are further limited to ST receptor ligands that are antibodies or portions thereof and active agents that include, but are not limited to, chemotherapeutics such as methotrexate, doxorubicin, 5-4 fluorouracil, etc (Claim 30). The method further comprises intravenous administration.

However, the specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed. First, the claims can broadly be interpreted as being drawn to a method of "preventing" a colorectal tumor in an individual because the claims do not require that the individual actually has a tumor- only that the individual is "suspected" of having a tumor. Those of skill in the art of oncology recognize that the state of the art of cancer prevention is relatively unpredictable, and most physicians would not recommend the preventive administration of antibodies with cytotoxins to individuals who have not been clinically confirmed to have a tumor. Furthermore, the specification teaches (page 12, line 10) that to "identify" those suspected of suffering from colorectal cancer, those individuals need to be "diagnosed" with colorectal cancer. Thus, absent evidence to the contrary, the method is only enabled for treating an individual that *has* colorectal cancer. Secondly, with regards to the general treatment of cancer with antibodies, the specification lacks working examples, and the nature of the invention is highly unpredictable as set forth below.

Those of skill in the art also recognize the unpredictability of treating tumors with antibodies. For example, Jain (Scientific American July 1994), discloses barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in

the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, in the late 80's, Dillman (Annals of Internal Medicine, Volume 111, pages 592-603, 1989) summarized (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). More recently, Weiner (Seminars Oncology, Vol. 26, No.4, 1999, pages 41-50) provided an overview of monoclonal antibody of therapy including some promising activity, however major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, insufficient target specificity, and induction of HAMA (page 43). The above obstacles are further compounded by the fact that, in this case, the target (ST receptor) is present on both normal and cancerous cells. Hence, according to one of the obstacles set forth by Weiner, there is a total lack of target specificity. For instance, the

claims are drawn to "treating" an individual suspected of suffering from colorectal cancer. This treatment necessarily includes administration of a ligand to the ST receptor along with a cytotoxin. However, the specification teaches (page 6, lines 1+) that expression of the ST receptor is *not limited* to colorectal cancer cells. For example, the specification teaches "In normal individuals, ST receptors are found exclusively in cells of the intestine, in particular in cells in the duodenum, small intestine (jejunum and ileum), the large intestine, colon (cecum, ascending colon, transverse colon, descending colon and sigmoid colon) and rectum." Thus, one of ordinary skill in the field of oncology would not expect the claimed invention to effectively treat a colorectal tumor because the treatment would also destroy healthy, normal cells of the intestine, colon, and rectum that also express the ST receptor. Thus, such a method, would effectively harm the individual instead of treating the individual. Further, the disclosure provides no objective evidence or working examples so that one of ordinary skill in the art would have a reasonable expectation of success in practicing the method. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer with antibodies. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that it would require undue experimentation to successfully practice the invention as claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23, 27-28, 30-32, 36 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 5, 10, 30-31 of U.S. Patent No. 5,879,656. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following:

US Patent 5,879,656 claims a method of treating an individual suspected of suffering from "metastasized" colorectal cancer comprising administering parenterally to said individual a pharmaceutical composition comprising a therapeutically effective amount of a conjugated compund comprising an ST receptor binding moiety; and, an active moiety; wherein said active moiety is a radiostable active agent that is a radiostable therapeutic agent. (The patent defines radiostable as "compounds which do not undergo radioactive decay, i.e. compounds that are not radioactive (column 4, line 36)). The claims are further drawn to active agents selected from the group consisting of methotrexate, doxorubicin, daunorubicin, etc. The claims are further drawn to wherein said ST receptor binding moiety is an antibody, FAB, or F(Ab), and wherein said ST receptor binding moiety is an antibody.

The currently pending claims are also drawn to a method of treating an individual suspected of suffering from colorectal cancer comprising administering to said individual an therapeutically effective amount of a pharmaceutical composition comprising an ST receptor

ligand, an active agent that causes cell death, and a pharmaceutically acceptable carrier or diluent. Thus, the claims of the '656 patent represent a obvious variation or species of the present claims in that the present claims encompass treating an individual suffering from a metastasized colorectal cancer. Also, there is no patentable distinction between radiostable agents and agents that cause cell death because the broadly claimed agents are considered radiostable and or cause cell death.

Claims 23 and 36 are further rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6-7, and 8 of U.S. Patent No. 6,060,037 for similar reasons as delineated above.

Claims 6-7, and 8 are drawn to a species of the currently claimed invention in that metastasized colorectal cancer is encompassed by claim 23 of the present invention. Furthermore, both active moieties of either claim 6 or 7 cause cell death as claimed in the instantly claimed application.

Claim Objections

Claim 30 is objected to because it is drawn to a non-elected claim. The claim recites "the method of claim 29", the latter claim being a non-elected claim.

Claims 31 and 32 are objected to under 37 CFR 1.75(c) because they appear to be of improper dependent form in that they fail to further limit the subject matter of a previous claim. Claims 30 and 31 are dependent from claim 30. They also appear to be similar in scope to claims

27-28- all of which are ultimately dependent from the independent claim, Claim 23. Clarification or amendments are requested.

Information Disclosure Statement

The information disclosure statement (Paper No. 3) was considered, in part. However, numerous references were either unavailable or not matched with the prior applications listed (i.e., 08/583447, 08/635930, 08/468449, 09/138,237). Although the Examiner has made efforts to obtain all of the references, it is suggested that Applicants endeavor to file the missing references.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
October 22, 2002

ANTHONY C. CAPUTA
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